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### Cochlear implantation in a profoundly deaf patient with MELAS syndrome

Cochlear implantation is now an established technology for restoring hearing in profoundly deaf patients. Adults who have lost all useful hearing in both ears are suitable for cochlear implantation if they are profoundly deaf (generally this implies hearing thresholds of 100 dB nHL or worse, across the frequency range 125 to 8000 Hz), with aided hearing thresholds worse than 60 dBA for the frequencies 250 to 4000 Hz and scoring less than 30% in a test of sentence discrimination, using their hearing aids and without lip reading. We describe a patient with MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes) who became profoundly deaf and who has successfully undergone cochlear implantation and rehabilitation.

A right handed secretary with MELAS syndrome, and a confirmed A to G mutation at nucleotide 3243 in the mitochondrial genome, was referred to the cochlear implant programme of The Royal National Throat, Nose, and Ear Hospital. She had insulin dependent diabetes, congenital cataracts, short stature, leg weakness, fatigue, and hearing loss. She had never had encephalopathy or strokes. Her mother is also diabetic, has glaucoma, and has a lesser degree of deafness, and her sister has been profoundly deaf from adolescence in addition to having severe mental retardation. The patient had begun to experience bilateral hearing loss at the age of 22, with slow deterioration up to the age of 29, by which time she was profoundly deaf in the right ear. By the age of 30 she was also profoundly deaf in the left ear and had developed tinnitus. She had no spontaneous vertigo, but sudden movements could leave her temporarily unsteady. At the age of 31 she was referred for assessment for cochlear implantation. Her ability to communicate with her family was severely restricted because of her deafness. She had developed a modest lip reading ability and was able to lip read her husband to a limited extent, but relied greatly on finger spelling and written information. Her own voice quality had begun to deteriorate. She was found to have no measurable hearing thresholds except for a 250 Hz tone at 105 dB nHL in the right ear. No tests of speech discrimination were possible, as she had virtually no hearing in either ear. Middle ear impedence was normal, and she had normal bilateral vestibular function on caloric testing. Auditory brain stem responses and electrocochleography showed no peaks in response to wide band clicks presented to either ear at 100 dB nHL, consistent with profound sensorineural deafness. Electrical stimulation of the cochlea, using sinusoidal stimuli presented through a transtympanic needle electrode placed through the tympanic membrane onto the promontory of the middle ear,[1 2] gave rise to a subjective sensation of hearing in both ears, with better performance on gap detection and temporal difference limen tests on the right. A CT scan of the temporal bones was normal.

The findings listed above showed her to be within the criteria for cochlear implantation, and she was implanted in the right ear at the age of 32 with a Nucleus 22 multichannel implant. All 22 electrodes were inserted into the cochlea and there were no surgical complications.

Subsequent switch on and rehabilitation went well, and the patient has made good progress. She is able to discriminate environmental sounds well, including different birdsongs, and participate in conversation. Verbal communication with her family has improved. There have been no specific problems with the implant and she is able to converse on the telephone using the implant. The patient has resumed full time work in an office. The tinnitus has remained stable, and there have been no vestibular problems. At the 2 year assessment she scored 97% correct on CUNY/UCL sentences (a British adaptation of a sentence discrimination test developed at City University, New York), using her implant and lip reading and 92% correct on BKB (Bamford, Kowal and Bench) sentences (another speech discrimination test) using her implant but without lip reading. Speech production was within normal limits, although the narrow pitch range reflected her slightly flat pattern of intonation.

MELAS syndrome was first described in 1984 and is one of a group of mitochondrial cytopathies, associated with point genetic mutations. In the brain the characteristic abnormalities are basal ganglia calcification and focal lesions of cerebellar and cerebral atrophy, resulting from cellular rather than vascular dysfunction.[3] Although it does not feature in the acronym, hearing loss is a common finding in MELAS. Reports of large kindreds and patient series have shown that at least 50% of patients have a moderate or severe sensorineural hearing loss: 21 of 28 patients with MELAS in an Australian series were deaf,[4] as were eight of 14 patients in a British series.[5] The phenotypic expression of the mutation is subject to at least three constraints; the percentage of mutant mitochondrial DNA in the target tissue (which has at most a loose correlation with clinical lesions),[5] the oxidative stress to which different organs or cell populations are exposed, and as yet unidentified collaborating somatic mutations which enhance selective aspects of the syndrome.

The cochlea is an organ exquisitely vulnerable to oxidative stress. The outer hair cells have a precarious, indirect metabolic support from Deiter cells, and the stria vascularis is both metabolically very active and non-mitotic, hence further subject to mutation accumulation. Recently detailed audiological findings have been reported in 18 patients with MELAS, and the authors argued that the hearing loss in their patients was entirely due to cochlear lesions.[4] There were excellent speech discrimination scores in six of 12 patients with mild to moderate deafness, and excluding severe and profoundly deaf patients with absent responses, there were normal and symmetric brain stem evoked responses in 18 of 20 latencies recorded from 10 patients. Promontory stimulation testing in two patients was normal, and CT and MRI were reported as showing no lesions which could contribute to hearing loss.

Central auditory lesions have been reported as a cause of hearing loss in MELAS. Imaging studies using both CT and MRI have shown that the occipital and parietal lobes and cerebellum are the brain regions most likely to show focal lesions,[3] and a perfusion study using $^{123}$I-IMP SPECT, and acetazolamide challenge, showed that patients with MELAS typically have hypoperfusion of the occipital and parietal lobes, with a significant defect in perfusion reserve.[6] A case report of a patient who died after having had severe seizures and stroke-like events, and who had had multiple imaging studies, showed mild temporal lobe atrophy at necropsy with associated spongy degeneration of the cortex.[7] All cortical regions were demonstrated radiologically and pathologically to be abnormal in this patient, with the occipital lobe showing the most marked hypoperfusion. She had become deaf 2 years before her marked clinical deterioration.

The patient we report has had no seizures or stroke-like episodes. Her presenting complaint was hearing loss, which progressed over 8 years to profound deafness. Her selection as a candidate for cochlear implantation was straightforward, and she has been successful in adapting to the device and has gained a significant benefit from it. The performance of the patient in the BKB word tests places her in the top 5% of adult performers in our patient series. Another patient with profound deafness and MELAS, who had had seizures and strokes, has recently been reported incidentally in a large series to have been implanted with a successful outcome, but unfortunately details were not provided.[4]

The fact that this patient has gained considerable benefit from her cochlear implant raises the possibility that other patients with MELAS syndrome and profound sensorineural deafness could benefit from this procedure.

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# CORRESPONDENCE

### Lead poisoning from complementary and alternative medicine in multiple sclerosis

In response to the article *Lead poisoning from complementary and alternative medicine in multiple sclerosis*,[1] we are very concerned that this

case has been blamed on homeopathic plumbum metallicum that the patient used in an attempt to improve the symptoms of multiple sclerosis. The original article states that he had used a homemade remedy; this is very unlikely to have been prepared using the strict regime applied by homeopathic laboratories. A correctly prepared remedy would only contain minute traces of lead, not enough to cause toxicity.

Certainly a likely explanation (acknowledged in the original article) would have been the lead contained in the pipe he had been using to smoke marijuana.

We consider it worrying when doctors who purport to use modern science to find answers to often difficult questions will, when it suits, simply make assumptions without appropriate testing of the hypothesis in question.

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## Anti-GQ1b IgG antibody syndrome without ophthalmoplegia: clinical and immunological features

I read with interest the review by Odaka *et al*[1] of the range of clinical disorders manifesting in patients with raised anti-GQ1b IgG antibodies. Their patients were classified into Miller Fisher syndrome, Bickerstaff's brain stem encephalitis, acute ophthalmoparesis without ataxia, Guillain-Barré syndrome, and "unclassified". The last group included patients who all had external ophthalmoplegia and normal tendon reflexes, and also varying degrees of limb, facial, and bulbar weakness. I have recently encountered a patient who developed an acute, sensory polyneuropathy in association with raised anti-GQ1b IgG antibodies, whose clinical features differ from the 194 patients described in their series.

A previously well 35 year old man had an episode of sore throat and dry cough, with associated myalgia and fever, in May 2000. Two weeks later, he developed tingling paraesthesia first in his feet, spreading up to his knees, and then in both hands. He found it difficult to distinguish where the ground was beneath his feet because of reduced sensation. One week into this illness, he developed partial drooping of his right eyelid. He had no symptoms of weakness or double vision. On examination 3 days later, he had a partial right ptosis, but eye movements were normal and he did not report diplopia. Muscle power and tendon reflexes were normal in all four limbs. He had a rather deliberate gait because of very mild sensory ataxia with reduced sensation to pain, light touch, and vibration sensation in both legs, to the level of the knees. Joint position sense was impaired in the toes but normal in the fingers.

Nerve conduction studies 3 weeks into his neurological illness showed normal distal motor latencies, proximal conduction velocities, and F wave latencies in all four limbs. All sensory nerve action potentials were absent. Protein in CSF was raised at 0.7 g/l (acellular sample). Coxsackie B IgG antibodies were raised at 1:64. Antiganglioside antibody assays showed raised IgG titres to GQ1b (1:8000), GD1b (1:11000), and GT1b (1:2200).Over the course of the next 2 weeks he improved without treatment, achieving full recovery with no residual symptoms or signs.

The lack of external ophthalmoplegia and ataxia was only encountered in patients classified as Guillain-Barré syndrome in the series by Odaka *et al*,[1] all of whom had limb weakness and reduced or absent reflexes. The electrophysiological findings in this patient were not compatible with criteria for demyelinating or axonal Guillain-Barré syndrome, but repeated studies can rarely be normal.[2] Electrophysiological studies on patients with Guillain-Barré syndrome with ophthalmoplegia and positive anti-GQ1b antibody titres have shown marked attenuation or absence of sensory nerve action potentials, suggesting that anti-GQ1b antibodies may be particularly involved in sensory nerve conduction failure.[3]

A recent report of eight cases of sensory Guillain-Barré syndrome has highlighted the existence of this variant.[4] Two of these patients had normal motor nerve conduction studies, one of whom had essentially normal tendon reflexes. Not all of these patients were tested for antiganglisoide antibodies.

The GQ1b ganglioside is present in both sensory and motor nerves, including oculomotor nerves,[5] and the range of disease associated with anti-GQ1b antibodies could theoretically involve dysfunction in any one or more of these types of nerves in varying degrees. If the screening of antiganglioside antibodies is extended to all patients with Guillain-Barré syndrome and its variants (with or without ocular signs) in a large series, then the clinical range associated with anti-GQ1b antibodies will no doubt expand to include more patients without marked ataxia or external ophthalmoplegia, as in this case.

I thank Dr Hugh Willison, Southern General Hospital, Glasgow, for performing antiganglioside antibody assays, and for helpful comments.

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*Odaka and Yuki reply:*

Maddison considered that clinical features of his patient were similar to those of "sensory Guillain-Barré syndrome", as proposed by Oh *et al*.[1] All of the patients of Oh *et al* had electrophysiological evidence of demyelination in at least two sensory nerves. By contrast, no evidence of demyelination in sensory nerves was shown in his patient. To produce the evidence, Maddison should have repeatedly performed sensory nerve conduction studies during the convalescent phase. Because sensory nerve action potentials were absent in his patient, the "syndrome of acute sensory neuropathy" as proposed by Windebank *et al*[2] may be the diagnosis.

We earlier reported on a patient with a relapsing form of the acute sensory neuropathy syndrome.[3] The patient rapidly developed marked sensory ataxia without ophthalmoplegia and limb weakness after an upper respiratory tract infection. The symptoms reached their maximum in a few days, followed by subsequent improvement over a few weeks. However, unsteady gait remained as a chronic deficit. Stepwise progression of his symptoms occurred over 15 years with 10 similar relapses. Sensory nerve conduction studies showed the absence of action potentials, and sural nerve biopsy showed the marked loss of large myelinated fibres. The patient's serum had an extremely high titre of an IgM monoclonal antibody directed against b series gangliosides GD2, GD1b, GT1b, and GQ1b. His IgM reacted neither with GD3 nor with GT1a. An absorption study showed that the anti-GQ1b IgM antibody cross reacted with GD2, GD1b, and GT1b.[4] The common sugar structure (NeuAc-α2–8-NeuAc α2–3 (GalNAc β1–4) Gal β) seems to be the binding site of the IgM antibody. Interestingly, serum IgG from the patient of Maddison reacted with GD1b, GT1b, and GQ1b, although whether his IgG had antibody activity against GD2 and GD3 was not shown. An absorption study would clarify whether his IgG reacted with a disialosyl residue linked to the internal galactose common to b series gangliosides. An immunohistochemical study showed localisation of GD1b in the neurons of the human dorsal ganglion. GD1b is also localised in the large neurons of the rabbit dorsal root ganglion, and Kusunoki *et al*[5] succeeded in the development of sensory ataxic neuropathy by sensitisation with GD1b. Autoantibody to b series gangliosides including GD1b may function in the development of acute sensory ataxic neuropathy in some patients.

Anti-GQ1b IgG antibody from patients with Miller Fisher syndrome cross reacts with GT1a. GT1a has a disialosyl residue linked to the external galactose common to GQ1b, and this may be the binding site of the autoantibody. We investigated the fine specificity of anti-GQ1b IgG antibody in serum samples from 82 patients: 56 with Miller Fisher syndrome, 11 with Guillain-Barré syndrome, 13 with Bickerstaff's brain stem encephalitis, and two with acute ophthalmoparesis. External ophthalmoplegia was present in all of these patients. Anti-GQ1b IgG antibodies were absorbed by GT1a in 80 (98%) of the 82 serum samples, by GD1b in 11 (13%), and by the other b series gangliosides GD3, GD2, or GT1b in 24 (29%). The most frequent pattern of fine specificity was the cross reaction with GT1a alone, seen in 56 (68%) samples. By contrast, we recently noted that some patients with the "ataxic form of Guillain-Barré syndrome" showed no or minimal external ophthalmoplegia but had anti-GQ1b IgG antibody. Anti-GQ1b IgG antibody from the patients, as well as those with Miller Fisher syndrome, were absorbed by GT1a. The finding that ataxic Guillain-Barré syndrome and Miller Fisher syndrome have in common an autoantibody with the same fine specificity suggests that they form a continuous range. We should not have used